Bone Morphogenic Protein

for the Treatment of Long Bone Fractures and for Use In Spinal Fusion Procedures

Department of Labor and Industries
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Introduction

Osteogenic proteins (OP) are elements of a class of natural growth factors called Bone Morphogenetic Proteins (BMP). The isolation of the genes coding these proteins from human DNA has identified a family of proteins, from BMP-2 to BMP-6, and from OP-1 to OP-3. (Miniscalco 2002)

Implantation of recombinant human BMP (rhBMP) induces bone formation by causing the differentiation of mesenchymal cells into chondroblasts and osteoblasts. To administer BMP locally, BMP is combined with an absorbable collagen sponge made from bovine Type I collagen. (Riedel 1999)

Several studies on OP-1 (rhBMP-7) and rhBMP-2 have been published. OP-1 has been used to treat long bone fractures as well as to aid in spinal fusions. OP-1 comes as a protein powder and is mixed with bovine bone collagen and sterile saline solution to form a paste. The paste is then placed between the broken ends of the bone during surgery.

rhBMP-2 is one component in a system used during spinal fusions for the treatment of degenerative disc disease. The InFUSE Bone Graft consists of rhBMP-2 and a bovine Type I collagen carrier. InFUSE Bone Graft is combined with the LT-CAGE lumbar tapered fusion device. The cage is intended to maintain spacing within the spine while the InFUSE Bone Graft is intended to form bone for spine stabilization. (FDA 2002)

Food and Drug Administration (FDA) Status

On October 17, 2001, the FDA granted Stryker Biotech approval for its OP-1 Implant under a humanitarian device exemption (HDE). The HDE is similar to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA. The application must allow the FDA to determine that the device does not pose a significant risk of illness or injury. Product labeling must state that the device is a humanitarian use device and that effectiveness of the device for the specific indication has not been demonstrated.

The OP-1 Implant is approved as an alternative to autograft in recalcitrant long bone nonunion where use of autograft is not feasible and alternative treatments have failed. (FDA 2001)

On July 2, 2002, the FDA granted Pre-Market Approval for Medtronic Sofamer Danek's InFUSE Bone Graft and LT-CAGE Lumbar Tapered Fusion Device system. The device is classified as "Protein, collagen scaffold with metal prosthesis, osteoinduction."

InFUSE Bone Graft and LT-CAGE Lumbar Tapered Fusion Device system is FDA indicated for patients with degenerative disc disease at one level from L4-S1. Degenerative disc disease is defined as discogenic back pain with degeneration of the disc confirmed by patient history, function deficit, or neurological deficit and radiographic studies. Patients could also have had Grade I Spondylolisthesis. The device is to be implanted via an anterior open or anterior laparoscopic approach. (FDA 2002)

BMP for the Treatment of Tibial Nonunion

I. Published Case Series Studies

a. Johnson's small case series attempted to enhance bone regeneration by augmenting autogeneic cancellous bone graft with human bone morphogenetic protein implants. (Johnson 1988)

The 6 cases experienced segmental tibial bone loss ranging from 3 to 17 cm. Five subjects had a history of infection. Four subjects had previous treatment with external factors, and 3 had failed previous autogeneic cancellous grafting. The same 3 patients had also failed pulsed electromagnetic bone growth stimulation.

The surgeons placed the rhBMP strip under the medial periosteal sleeve of the defect while autogeneic cancellous bone filled the intercalary defect between the proximal and distal shaft fragments.

The following grades were used to assess outcome.

Anatomic Grade	Economic Grade	Functional Grade
A0 – pseudoarthrosis	E0 – complete invalid	F0 – motion at the fracture site
A1 – unilateral pseudoarthrosis	E1 - no gainful employment	F1 – level of pain is same as before operation, but able to perform all activities of daily living (ADL)
A2 – insufficient unilateral bone mass	E2 - able to work, but did not return to previous occupation	F2 – occasional extremity pain and able to perform ADL
A3 – contiguous union without hypertrophy	E3 - returned to previous occupation on a part-time or limited status	F3 - no pain and able to perform all ADL except sports
A4 - solid union	E4 - returned to previous occupation without restrictions	F4 – complete recovery, no recurrent episodes of pain, and unrestricted activity

Results: Five patients healed without further surgical treatment. No patients experienced allergic reactions.

Tibial Segmental Defects Implanted with Bone Morphogenetic Protein (rhBMP)

Case no.	Age (yr)	Defect size (cm)	Preoperative Duration (months)	Healing Time (months)	Results	Follow-up (months)
1	22	13	8.1	5	A4/E4/F4	38.3
2	22	8	5.1	4	A4/E4/F4	39.3
3	35	3	60.4	5	A4/E4/F3	27.6
4	35	4	19.2	5	A4/E4/F4	14.6
5	35	17	6.7	9	A4/E1/F3	24.2
6	42	5	42.1	6	A4/E4/F4	19.5

Conclusion: rhBMP can be implanted without any adverse effects.

b. Johnson's second case series study examined rhBMP implantation for the treatment of distal tibial metaphyseal nonunions with residual anterior cortical bone loss. (Johnson 1990)

The four patients in the study underwent reduction and fixation of the posterior tibial cortex. Then, rhBMP implants were positioned across the anterior tibial cortical defect in contact with the residual freshened bone of the distal tibial metaphysis.

Study Population: The 4 patients had open tibial fractures. Each tibia had significant posterior bowing deformities averaging 42 degrees and associated valgus deformities averaging 6 degrees. Malunion of the fibula with bony overgrowth prevented manual correction of the tibial deformity. The patients failed an average of 5.8 previous surgical procedures, including 6 plate stabilizations and 7 autogeneic cancellous iliac crest bone grafts.

Results: All 4 nonunions united at an average of 4.4 months. Posterior bowing was reduced to 0 degrees in 3 patients. Ankle dorsiflexion averaged 9 degrees and plantar flexion averaged 18 degrees. Subtalar motion ranged from 50% to 70% in three patients.

Case no.	Preoperative Duration (months)	Healing Time (months)	Results	Follow-up (months)
1	36	4.0	Very good	57
2	32	4.0	Fair	38
3	14	4.5	Good	27
4	17	5.2	Very Good	10

Before the procedure, no patient ambulated without crutches. After the procedure, two subjects attained unlimited daily living function and returned to full employment. One patient ambulated with a cane after surgery.

Conclusion: Although a randomized double-blind consecutive series of matched cases is necessary to prove the efficacy of rhBMP, implants of rhBMP combined with skillful surgical treatment are under investigation in the interim as an alternative to amputation.

c. Riedel conducted a case series study examining the effect of rhBMP-2 on extra-articular, open tibial fracture with a Gustilo-Anderson classification of II or higher. (Riedel 1999)

Patient underwent surgical procedures that included fracture reduction within 24 hours of injury, repeated wound debridement, and fracture coverage within 14

days of the injury. Clinical and radiographic evaluations of the fracture site occurred at 1 and 6 weeks and at 3, 4, 6, and 9 months.

Study Population: The study included 12 patients with a mean age of 37 years. They had sustained open tibial fractures from motor accidents (10), gun shot wounds (1), and industrial accidents (1).

Patients were excluded due to infection, planned use of bone graft, history of bone disease, or drug use affecting bone metabolism.

Results: The median time between injury and rhBMP-2/ACS implantation was 4 days.

Eleven patients completed 9-month follow-up. Fractures in 9 patients healed without further intervention. The remaining three patients required second surgical interventions for delayed union and underwent bone grafting 16 to 17 weeks following injury.

Two patients experienced positive antibody titers to rhBMP-2. These responses were not detected at 14 weeks and were not associated with other clinical manifestations.

Five infections were detected in four patients. The pin of the external fixation device on the contralateral leg impaled a patient's treated limb. Infection was also due to cellulitis at the skin/muscle graft and infection at the site of the dynamic compression plate.

Conclusion: Data from the pilot feasibility study have demonstrated that implantation of rhBMP-2 combined with an absorbable collagen sponge is surgically feasible and safe.

II. Published Randomized Controlled Trials

a. Friedlaender conducted a prospective, randomized, partially blinded clinical trial under the FDA approval process. Tibial nonunions were treated with intramedullary fixation and implantation at the fracture site of OP-1 in a collagen carrier or bone autograft. (Friedlaender 2001)

The researchers measured pain at the fracture site (none, mild, moderate, severe) and the ability to bear weight (none, partial, full). The study defined clinical success as full weight bearing, less than severe pain at the fracture site on weight-bearing, and no further surgical intervention.

Other measurements included time of surgery, estimated blood loss, hospital length of stay, degree of pain at donor site, and antibodies to OP-1 and type I

collagen. In addition, 3 blinded radiologists independently assessed whether bridging by new bone existed across the fracture site.

Follow-up occurred at 1, 2, 3, 6, 9, 12, and 24 months. The primary endpoint was at 9 months.

Study Population: The study enrolled 122 patients with 124 tibial nonunions. Nonunion was defined as 9-month duration of the nonunited fracture with no evidence of progressive healing over the previous 3 months.

All 122 patients underwent intramedullary (IM) rod fixation. 61 patients with 63 tibial nonunions were randomly assigned to receive OP-1 on a Type I collagen carrier at the fracture site. The other 61 patients with 61 tibial nonunions received bone autograft.

The study excluded patients who were candidates for internal fixation alone (generally reaming and an intramedullary rod). Patients were also excluded due to infection, severely compromised soft tissue coverage at the nonunion site, pathological fracture, radiation therapy, chemotherapy, immunosuppression or chronic steroids, congenital or synovial pseudoarthrosis, neuropathy, nonunion of multiple bones, autoimmune disease, or sensitivity to collagen.

Demographic Data

	OP-1 (n=63)	Autograft (n=61)
Median nonunion duration (months	17	17
*Atrophic nonunion (%)	41	25
Comminuted fracture at injury (%)	67	56
Open fracture at injury (%)	58	57
Grade III, IIIa, IIIb, or IIIc fracture at injury (%)	30	36
Prior autograft (%)	43	31
Prior IM rod (%)	54	44
Tobacco/nicotine use (%)	74	57
Mean age (years)	38	34
Mean weight (pounds)	171	187

*significant

Results: All patients in the autograft group had pain at the donor site following surgery, and more than 80% rated their pain as moderate or severe. More than 20% of patients had mild or moderate pain at 6 months, and 13% had persistent pain at 12 months.

81% (51 of 63) of the OP-1 group and 85% (52 of 61) of the autograft group had successful outcomes. Both groups demonstrated an 82% success rate at 24 months (37/45 of OP-1, and 31/38 of autograft).

At 9 months, 5% of the OP-1 group and 10% of the autograft group required surgical retreatment. At 9 months, bridging in at least 3 of 4 radiologic views was observed in 62% of the OP-1 group and 74% of the autograft group.

Researchers detected antibodies against type I collagen 5% of the OP-1 patients. Anti-OP-1 antibodies developed in 10% of OP-1 patients. No adverse events related to sensitization were reported.

Comparison of Operative Time, Blood Loss, and Hospital Length of Stay

	OP-1 (n=61)	Autograft (n=61)
*Operative Blood Loss (ml)	254	345
Length of Stay (days)	3.7	4.1
Operative Time (minutes)	169	178

*statistically significant

Conclusion: rhOP-1 (BMP-7) implanted with a type I collagen carrier was a safe and effective treatment for tibial nonunions. This molecule provided clinical and radiographic results comparable with those achieved with bone autograft without donor site morbidity.

b. Miniscalco conducted a small randomized-controlled pilot study to examine the effect of OP-1 with a monolateral external fixator on fresh tibial closed fractures. (Miniscalco 2002)

Surgeons treated 14 patients with Type A1 or A2 closed fracture of the tibial shaft with monolateral external fixator. Then, half the patients were randomly assigned to receive OP-1 at the fracture site.

The researchers confirmed fracture union by the absence of pain and motion at the fracture site. Fracture union also resulted in the presence of callus bridging on radiography. Patients underwent ultrasound, as well as blood and urine tests.

Radiographs were taken at 1, 2, 4 and 5 months.

Study Population: Patients were excluded due to open fractures, pathologic fractures, vascular lesions, or nerve lesions.

Demographic data

	OP-1	Control
Average age (years)	47	40
Average time from injury to surgery (days)	6	6.7

Results:

Comparison of Outcomes between Treatment Groups

	OP-1	Control
Average hospital stay (days)	11.7	12
Average time to partial weight bearing (days)	19	21
Average time to clinical and radiological fracture union (days)	135	131
Average time to fixator removal (days)	169	151

Blood and urine tests from the OP-1 Group did not show variations in calcemia, phosphoremia, calciuria, or phosphaturia. A progressive increase in alkaline phosphatase was noted in 6 cases. The researchers did not observe any adverse immunologic or allergic reactions.

Conclusion: Despite the low number of patients treated with OP-1, it is not indicated for fresh shaft fractures of tibia. The average healing times observed in the OP group were analogous to those observed in the control group.

c. Govender conducted a study to determine whether rhBMP-2 on an absorbable type I collagen sponge resulted in an increased rate of fracture-healing as evidenced by a reduction in the number of secondary interventions and by clinical and radiographic assessments. (Govender 2002)

The prospective, randomized controlled, single-blind study was conducted at 49 centers in 11 countries. Based on the Gustilo-Anderson classification of open wounds, patients were randomized to:
1. control - standard of care only (intramedullary nail fixation and routine soft tissue management)
2. standard of care and implant containing .75 mg/ml of rhBMP-2
3. standard of care and implant containing 1.50 mg/ml of rhBMP-2

The primary study efficacy end point was proportion of patients who received secondary interventions within 12 months after definitive wound closure.

Researchers defined a healed fracture as fulfillment of clinical criteria, including full weight-bearing and lack of tenderness at the fracture site on palpation, as well as radiographic evidence of fracture union. Two of 3 blinded, independent radiologists must have reported cortical bridging and/or disappearance of the fracture lines on at least 3 of 4 cortices viewed on anteroposterior and lateral radiographs.

Treatment failure was defined as a recommendation for a secondary intervention.

Researcher assessed safety via adverse event monitoring. They also measured patient antibody response to rhBMP-2 and bovine Type I collagen by serum sampling at baseline, 6 weeks, and 20 weeks.

Follow-up occurred at 6, 10, 14, 20, 26, 39, and 52 weeks.

Study Population: The study enrolled 450 patients with open tibial fractures. Definitive fracture fixation with intramedullary nailing was performed no later than 14 days after injury. The median time from injury to wound closure was 3 days.

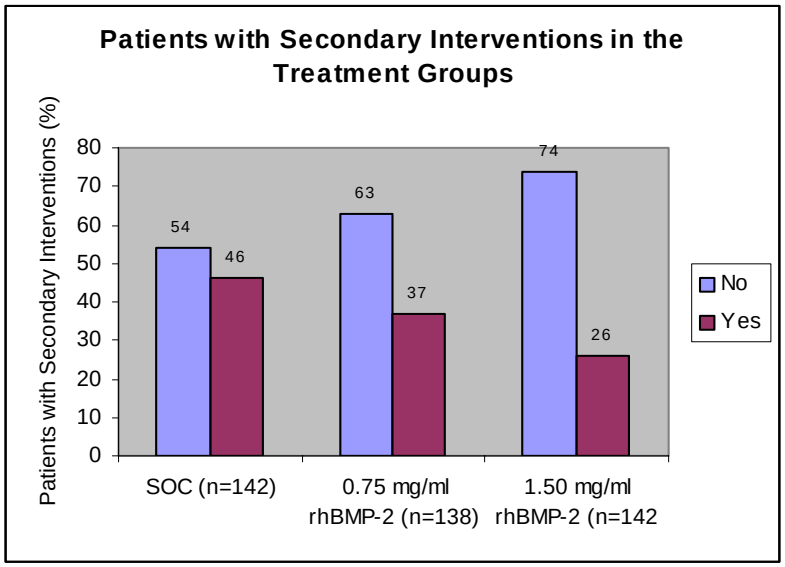
37 (8%) patients had concomitant fixation of the ipsilateral fibula. 59 (41%) patients in the 1.5 mg/ml rhBMP-2 group underwent reamed intramedullary nailing compared to 39 (27%) patients from the control group.

Demographic data

Characteristic	Standard Care	0.75 mg/ml rhBMP-2	1.5 mg/ml rhBMP-2
Randomized pop			
No. of patients	150	151	149
Mean age	37	37	33
Intent to treat pop			
No. of patients	147	145	145
Recent tobacco use	66 (45%)	73 (50%)	75 (52%)
Gustillo Anderson Type			
I	34 (23%)	29 (20%)	32 (22%)
II	54 (37%)	51 (35%)	50 (34%)
IIIA	42 (29%)	43 (30%)	38 (26%)
IIIB	17 (12%)	22 (15%)	25 (17%)

Results: 421 (94%) patients completed 12-month follow-up.

rhBMP-2 implant patients showed a significant, concentration-dependent decrease in the number of secondary interventions needed to promote healing. Analysis did not include 5 control, 7 0.75 mg/ml rhBMP-2, and 3 1.50 mg/ml rhBMP-2 patients due to lack of clinical outcomes data.



Both reaming and rhMP-2 independently affected the primary outcome. The rate of secondary interventions in the 1.5 mg/ml rhBMP-2 group after adjusting for reaming was significantly lower than in the control group.

Baseline Gustilo-Anderson classification predicted outcome. More severe (Type IIIB) wounds were twice as likely to have a secondary intervention than less severe wounds (Type I, II, IIIA).

Smoking history in the control group was associated with a 33% increase in the risk of secondary interventions (52% compared with 39% in nonsmokers). Among smokers, 30% of patients in the 1.5 mg/ml rhBMP-2 group required secondary intervention compared to 52% of control patients.

Fracture healing was observed in 50% of the patients at 184, 187, and 145 days in the control, 0.75 mg/ml rhBMP-2, and 1.50 mg/ml rhBMP-2 groups, respectively.

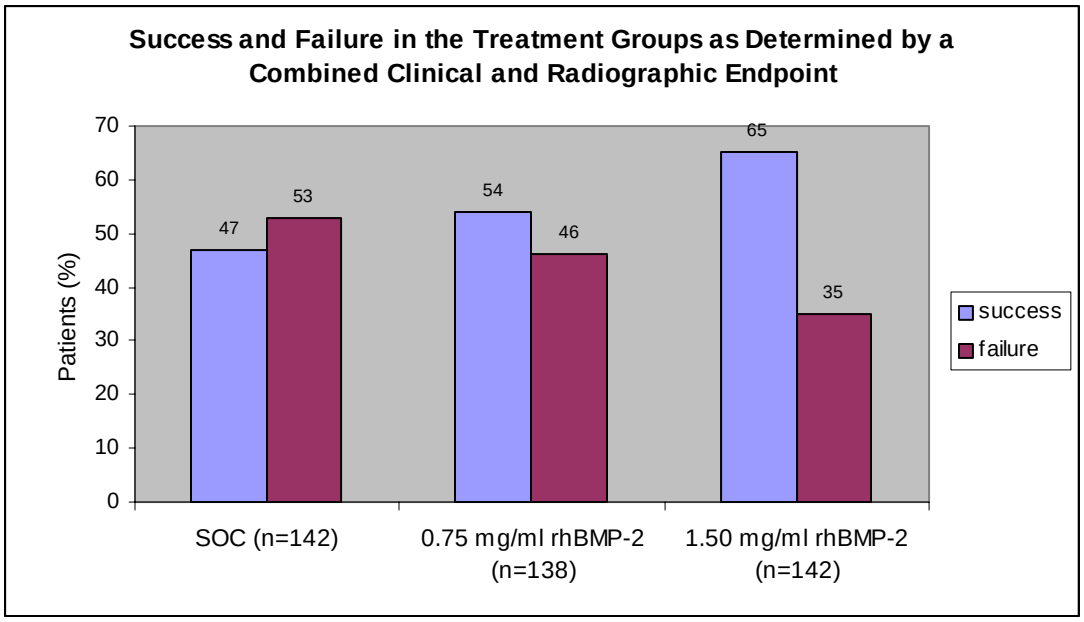
Comparison of Outcomes between Treatment Groups

	Standard Care	0.75 mg/ml rhBMP-2	1.5 mg/ml rhBMP-2
Infection			
Gustilo-Anderson I and II	13/88 (15%)	12/80 (15%)	15/70 (21%)
*Gustilo-Anderson IIIa and IIIb	26/59 (44%)	19/65 (29%)	15/63 (24%)
*Hardware failure	32/147 (22%)	25/145 (17%)	16/145 (11%)
*Wound healing, 6 weeks	90/138 (65%)	100/139 (72%)	117/141 (83%)
*Pain (all body systems)	116/147 (79%)	97/145 (67%)	98/145 (68%)

*statistically significant

Comparison of Antibody Detection among Treatment Groups

	Standard Care	0.75 mg/ml rhBMP-2	1.5 mg/ml rhBMP-2
Antibodies to BMP-2	1 (1%)	3 (2%)	9 (6%)
Antibodies to type-I bovine collagen	9 (6%)	22 (15%)	29 (20%)



Conclusion: rhBMP-2 implant was safe and, when 1.50 mg/ml was used, significantly superior to the standard of care in reducing the frequency of secondary interventions and the overall invasiveness of the procedures, accelerating fracture and wound-healing, and reducing the infection rate in patients with an open fracture of the tibia.

BMP for the Treatment of Femoral Nonunion

I. Published Case Series Studies

a. Johnson conducted a case series examining 12 patients with intractable nonunion of the femoral diaphyseal or metaphyseal-diaphyseal shaft. The BMP was used to aid in fracture union and was positioned in the perinonunion area.

The following grades were used to assess outcome.

Anatomic Grade	Economic Grade	Functional Grade
A0 – pseudoarthrosis	E0 – complete invalid	F0 – motion at the fracture site
A1 – unilateral pseudoarthrosis	E1 - no gainful employment	F1 – level of pain is same as before operation, but able to perform all activities of daily living (ADL)
A2 – insufficient unilateral bone mass	E2 - able to work, but did not return to previous occupation	F2 – occasional extremity pain and able to perform ADL
A3 – contiguous union without hypertrophy	E3 - returned to previous occupation on a part-time or limited status	F3 - no pain and able to perform all ADL except sports
A4 - solid union	E4 - returned to previous occupation without restrictions	F4 – complete recovery, no recurrent episodes of pain, and unrestricted activity

Study Population: The 12 patients had an average age of 48.4 years. The average duration of nonunion was 31.6 months. All patients had roentgenographic discontinuity gaps with abnormal mobility and pain. Eleven patients had previously failed 43 procedures and pulsed electromagnetic field bone growth stimulation.

Seven patients were stabilized with plate osteosynthesis and five received intramedullary nailing.

Results:

Femoral Nonunions Implanted with Bone Morphogenetic Protein (BMP)

Case no.	Age (yr)	Preoperative Duration (months)	Healing Time (months)	Results	Follow-up (months)
1	45	8.9	4	A4/E1/F3	42.4
2	67	68.3	Not healed		
3	68	60.2	5	A4/E3/F3	37.1
4	47	48.2	4	A4/E4/F3	43.1
5	16	12.9	6	A4/E4/F4	48.9
6	40	20.8	5	A4/E4/F4	30.8
7	38	43.4	3	A4/E4/F4	29.6
8	30	48.0	5	A4/E4/F4	15.5
9	75	22.4	4	A4/E3/F3	15.0
10	68	11.1	5	A4/E4/F4	16.4
11	48.8	20.3	4	A4/E4/F4	12.2
12	38	14.6	5	A4/E4/F4	9.8

Conclusion: The researchers believe that BMP favorably influenced the healing in 11 of 12 patients. However, the application of principles of adequate fixation and immobilization must also be fulfilled.

b. Johnson conducted a case series following 30 patients with femoral diaphyseal or diaphyseal-metaphyseal reconstructions augmented with rhBMP and allogeneic, autolysed antigen free bone carrier alloimplants. (Johnson 2000)

Patients with shortened femoral nonunions underwent standard deformity correction and restoration of the mechanical axis. In addition, the nonunions were lengthened with a one-stage distraction creating an intercalary defect at the nonunion site.

The rhBMP allograft bridged the medial aspect of larger intercalary defects greater than 2 cm. Autograft material was required to bridge these defects and allow host bone induction and remodeling.

Study Population: The study included 24 shortened atrophic femoral nonunions, 4 equal length atrophic nonunions, and 2 longstanding shortened malunions. Patients had an average age of 47 years. There was an average of 2 previous failed procedures per patient and an average of 2 failed autogenous cancellous bone graftings per patient.

The average time from initial femoral fracture to rhBMP implantation was 39 months.

Thirteen patients received additional autogeneic cancellous bone grafts to the intercalary segmental defect after one-stage lengthening. The interface between the implant and the host bone above and below the defect was not in contact with any cancellous graft material.

Results: Two subjects were lost to follow-up, which averaged 58 months. 24 of 30 femoral healed with rhBMP allogeneic implants and plate osteosynthesis.

The average time to healing was 6 months and average increase in length was 2.7 cm. The mean percentage of increased length over the pre-treatment shortened femur was 7%.

Six patients had fatigue failure of the plate implant. Of these 6 patients, 4 patients underwent revision surgery due to persistent distal metaphyseal nonunions. Three patients required additional cancellous grafting to the anterior and posterior aspects of the intercalary defects at an average of 5 months after lengthening.

Conclusions: The allogeneic, autolysed antigen free bone is an excellent carrier and bone graft material because it is human bone.

BMP for use in Spinal Fusion Procedures

I. Published Randomized Controlled Trials

a. Burkus compared the clinical and radiographic outcomes at 24 months of 279 patients who underwent a single-level ALIF with a tapered fusion device and either rhBMP-2 on an absorbable collagen sponge carrier or autogenous iliac crest bone graft. (Burkus 2002) [1] The study was conducted as part of the FDA's PMA process.

Data from the Oswestry Low Back Pain Disability Questionnaire, neurologic status, work status, patient satisfaction, back, leg, and graft-site pain questionnaires were collected at 6 weeks, and 3, 6, 12, and 24 months.

Two blinded radiologists examined radiographs and CT scan. The study defined a successful fusion as meeting all of the following:
1. bridging trabecular bone connecting the two vertebral bodies either through the dowels or around the dowels
2. no angular motion of 5 degrees or more
3. no sagittal translation of more than 3 mm
4. no radiolucencies that involved more than half of the interfaces between the dowels and the host vertebral end plates

Neurologic success was based on demonstrating maintenance or improvement in motor function, sensory function, deep tendon reflexes, and sciatic tension.

Subject Population: All patients had disabling symptoms for a minimum of 6 months and failed nonoperative treatment. They had single-level lumbar degenerative disc disease with primary symptoms of low back pain with or without leg pain or sciatica.

Results: Out of 20 points, the control group experienced donor hip site pain after surgery with a mean score of 12.7. At 24 months, nearly one-third of the control patients still experienced pain, averaging 1.8 points. 16% of patients were bothered by the appearance of the graft site.

	rhBMP-2	Autograft Group
Mean operative time (hours)	1.6	2.0
Average blood loss (mL)	109.3	153.8
Average hospital stay (days)	3.1	3.3

[1] Other studies from Burkus on rhBMP-2 have also been published in peer-reviewed literature. (Appendix A)

At all postoperative visits, average disability scores in both groups showed statistical improvement compared with preoperative scores. 84.6% of rhBMP-2 patients and 85.6% of control patients improved at least 15% in their disability scores at 12 months. 84.4% of the investigational group and 82.4% of controls improved at 24 months. At 24 months, the mean improvements in Oswestry scores were 29.0 points in the investigational group and 29.5 points in the control group.

At 12 and 24 months, the overall neurologic success rates for the investigational group was 81.8% and 82.8% compared with 84.7% and 83.3% rates for the control group.

	n		Back Pain Improvement		Leg Pain Improvement	
	rhBMP-2	Autograft	rhBMP-2	Autograft	rhBMP-2	Autograft
preop	143	136	15.8	16.1	12.5	12.5
3 months	140	134	8.7	9	6.8	6.8
6 months	136	131	8.6	8.9	6.3	6.3
12 months	129	125	8	8.4	6.3	6.6
24 months	122	108	7.3	7.9	6.5	5.9

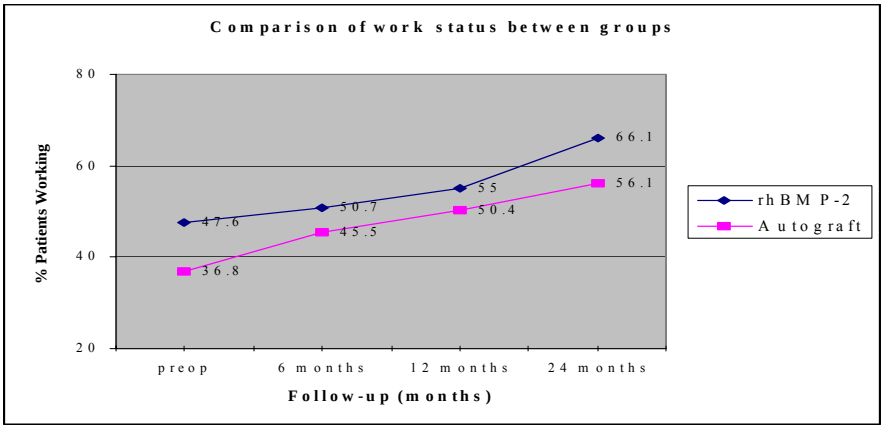
Number and Percentage of Successful
Radiographic Fusions by Treatment Group

	rhBMP-2	Autograft
6 months	128/132 (97)	115/120 (95.8)
12 months	127/131 (96.9)	112/121 (92.6)
24 months	120/127 (94.5)	102/115 (88.7)

For patients who were working before surgery, the median return to work time was 63.5 days in the investigational group and 64.5 days in the control group. More people from both groups were working at 2-year follow-up than were working before their surgery.

Number and (%) of patients by work status, treatment group, and followup

	rhBMP-2			Autograft		
	Working	Not working	Not working before surgery	Working	Not working	Not working before surgery
3 months	54 (38.3)	42 (29.8)	45 (31.9)	38 (28.4)	43 (32.1)	53 (39.6)
6 months	69 (50.7)	25 (18.4)	42 (30.9)	60 (45.5)	29 (22.0)	43 (32.6)
12 months	72 (55.0)	20 (15.3)	39 (29.8)	63 (50.4)	19 (15.2)	43 (34.4)
24 months	80 (66.1)	11 (9.1)	30 (24.8)	60 (56.1)	13 (12.1)	34 (31.8)



At 24 months, 81.2% of investigational patients and 80.4% of the controls were satisfied with their surgical outcomes.

Eleven patients (7.0%) in the investigational group and 14 patients (10.3%) in the control group had second surgeries, including implant removal and supplemental fixation.

Six rhBMP-2 patients and 5 autograft patients experienced vascular events. Eight adverse events occurred related to harvesting of the iliac crest graft, including injuries to the lateral femoral cutaneous nerve, avulsion fractures of the anterior superior iliac crest, infection, and hematoma.

The researchers did not observe negative consequences to positive antibody test results.

Conclusion: The use of rhBMP-2 is associated with high fusion rates without the need for harvesting bone graft from the iliac crest and exposing the patient to the adverse effects associated with that procedure.

b. Boden examined rhBMP-2 in a study allowed under the FDA's Investigational Device Exemption. (Boden 2002) [2]

The study's primary determinant for effectiveness was achievement of a solid posterolateral lumbar spine fusion. Fusion was defined as bilateral continuous bridging of trabecular bone, less than 3 mm of translation, and less than 5 degrees of angular motion on lateral flexion-extension radiographs. Two masked independent neuroradiologists assessed outcomes.

The study also measured scores from the Oswestry Low Back Pain Disability Questionnaire, SF-36, and a 10-point VAS for pain duration and pain intensity for

[2] Studies affiliated with Boden's FDA study have also been published in peer-reviewed literature. (Appendix B)

back, leg, and hip. Neurologic status was based on motor, sensory, reflex, and straight-leg-raise tests.

Researchers monitored adverse events, which were defined as any clinically adverse sign, symptom, syndrome, or illness that occurred or worsened during the operative or postoperative period of the trial, regardless of causality.

Antibody formation to the rhBMP-2 was measured at 3 months. Readings above 50 titers positively indicated antibody presence.

Follow-up occurred at 1.5, 3, 6, 12, and 24 months.

Study population: The study randomized 27 patients undergoing single level posterolateral lumbar arthrodesis. Using a 1:2:2 ratio, patients were assigned to one of three treatments:
1. autogenous iliac crest bone graft with Texas Scottish Rite Hospital pedicle screw instrumentation (TSRH) (n=5)
2. rhBMP-2/TSRH (n=11)
3. rhBMP-2 only with no instrumentation (n=11)

The study included patients with single-level degenerative disc disease whose Oswestry scores were greater than 30. Patients failed nonoperative treatment for at least 6 months. In addition, radiographic studies showed one or more of the following:

- instability defined as angular motion greater than or equal to 5 degrees or translation greater than or equal to 4 mm based on flexion-extension lateral radiographs
- osteophyte formation
- decreased disc height
- thickening of ligamentous tissue
- disc degeneration or herniation
- facet joint degeneration
- spondylolisthesis

Patients were excluded due to previous spinal fusion at same level, fusion of more than one level, medications that interfere with fusion, osteopenia, osteoporosis, osteomalacia, malignancy, infection, obesity (40% over ideal body weight), titanium allergy, prisoner status, tobacco use at time of surgery, history of autoimmune or endocrine disorder, or previous exposure to BMP.

Demographic Information

	Autograft/TSRH	BMP-2/TSRH	BMP-2 only
Patients	5	11	9
Age	52.9	57.6	51.8
Education (%>high school)*	40	100	87.5
Workers' compensation (%)	20	9.1	0
Tobacco used (%)	20	0	12.5

Alcohol used (%)	40	54.5	25
Previous back surgery (%)	0	27.3	12.5
Diabetes (%)*	40	0	0

* statistically significant

Results: Two patients from the BMP-2 only group were excluded from analysis because they had greater than Greater I spondylolisthesis on their preoperative lateral radiographs. Conclusions did not differ when the researchers ran the analyses with and without the two excluded patients.

Outcomes Comparing Treatment Groups

	Autograft/TSRH	BMP-2/TSRH	BMP-2 only
Patients	5	11	9
Operating Room Time (hours)	3.1	3.7	2.0
Blood Loss (mL)	430	577.3	333.3
Hospital Length of Stay (days)	4.4	3.3	4.0
Radiographic Fusion			
Number of patients (%)	2 (40%)	11 (100%)	9 (100%)

The BMP-2 only group had a statistically lower mean operative time compared to other groups. Researchers detected statistically significant differences between control and treatment groups on radiographic fusion rates.

Time by which Treatment Group Reached
Statistically Significant Improvement on Outcome Scales

	Autograft/TSRH	BMP-2/TSRH	BMP-2 only
Oswestry Disability	6 months	3 months	6 weeks
Bodily Pain index of SF-36	6 months	3 months	6 weeks

Improvement in back pain scores at latest follow-up were statistically significant for all three groups. The rhBMP-2 only group achieved the lowest mean back pain score. Improvement in leg pain scores at latest follow-up was statistically significant for only the rhBMP-2 only group.

Mean pain at the bone graft donor site decreased from 16.0 at the time of hospital discharge to 5.2 at the most recent follow-up assessment.

The rhBMP-2 only group showed the highest patient satisfaction. Autograft and rhBMP-2/TSRH groups showed similar levels of satisfaction.

One patient in the BMP-2/TSRH group who had leg pain underwent a decompression one level above the previous surgery. Another BMP-2/TSRH patient had an epidural hematoma evacuated 5 days after surgery. One patient in the BMP-2 only group with persistent back and leg pain underwent ALIF at 8 months. Another BMP-2 only patient had a superficial hematoma requiring evacuation 4 days after surgery.

22 rhBMP-2 patients and 4 autograft patients underwent antibody testing. The incidence of authentic anti-rhBMP-2 antibody formation was 4.5 % in the

rhBMP-2 group and 0% in the autograft group. The one patient with the positive antibody had a subsequent sample drawn, and the result was negative.

Conclusion: Statistically greater and quicker improvement in patient-derived clinical outcome was measured in the rhBMP-2 groups.

c. Johnsson conducted a trial randomizing patients in blocks of 6 to examine the effect of OP-1 on fusion outcomes. (Johnsson 2002)

The study included 20 patients randomized to fusion with either the OP-1 Implant or autograft bone from the iliac crest. Two OP-1 products were used in OP-1 patients, one on each side of the spine. The autograft bone was harvested through the initial midline skin incision from the dorsal part of one iliac crest.

Researchers conducted radiostereometric analysis in supine and standing positions monthly during the first 6 months after surgery. At 1 year after surgery, conventional radiography with anteroposterior and lateral views were performed. Bone formation was classified as bilaterally bridging bone, partial but not bilaterally bridging bone, or no bone formation.

Patients evaluated their outcomes as no back pain, minor back pain without regular need of analgesics, or major back pain with regular need of analgesics.

Researchers also noted treatment complications.

Study Population: Ten subjects received the OP-1 Implant and 10 subjects received autograft bone from the iliac crest. The mean age of the patients was 42 years.

The study included patients with L5 spondylolysis, maximal vertebral slip of 50%, 6 months intractable lumbosacral pain refractory to nonsurgical measures, and without radiating leg pain necessitating decompressive surgery.

Results: Neither group experienced faster L5 stabilization. At 1 year, the autograft group had a higher number of cases with stabilization of the L5 translations along the vertical axis.

Number of Patients by Outcome and Treatment Group at 1-year Follow-up

	OP-1	Autograft
Bone Formation		
bilaterally bridging bone	6	8
partial bone formation	3	2
no bone formation	1	0
Back Pain		
no back pain	4	5
minor back pain without regular need of analgesics	4	2
major back pain with	2	3

regular need of analgesics		

No intraoperative complications or adverse events occurred. Two OP-1 patients underwent reoperation.

Conclusion: No significant difference was noted between the radiostereometric and radiographic results of fusion with the OP-1 implant and fusion with autograft bone. The OP-1 implant did not yield better formation of stabilizing bridging bone than autograft bone in noninstrumented posterolateral lumbar fusions.

Cost and Insurance Coverage

In 1997, Perry presented cost data of treatment with OP-1 compared autograft for tibial nonunion. The average cost of OP-1 treatment equaled $12,468. In contrast, the average cost of autograft was $12,755. (Perry 1997)

"The quantity of InFUSE needed for an average spinal fusion will cost approximately $3000. Given that the procedure can cost $10,000 to $15,000, the new technology will increase expenses by 20% to 30%." (HAYES 2003)

On May 07, 2002, Aetna began covering the OP-1 Implant osteogenic protein for use as an alternative to autograft in recalcitrant long-bone nonunions where the

1) use of autograft is unfeasible and
2) alternative treatments have failed.

Autograft use may be deemed unfeasible because the patient:

- Had a previous autograft, and tissue is no longer available;
- Does not have sufficient autogenous tissue for the intended purpose;
- Is advanced in age (> 65 years) or obese;
- Shows morbidity (pain, infection, or fracture) at autograft donor site;
- Has excessive risk of anatomic disruption (including fracture) from harvesting autograft from donor site;
- Has poor bone quality (osteoporosis);
- Has concurrent medical conditions and comorbidities that increase the risk of autograft.

The OP-1 Implant is <u>not</u> covered for patients:

- with hypersensitivity to the OP-1 Implant or to collagen;
- who are skeletally immature (< 18 years of age or no radiographic evidence of closure of epiphyses);
- who are pregnant;
- with history of malignancy.
- who have resected tumors at or near the nonunion. (Aetna 2002)

In February 2003, BlueCross BlueShield of Nebraska announced coverage of BMP only when it is used with a cage, used with a threaded bone dowel, or used with femoral ring allografts. (BCBS 2003)

The Regence Group instituted the following policy in December 2002. Bone morphogenic protein may be considered medically necessary for the following indications:

1. With tapered lumbar fusion cages in single-level anterior lumbar spine fusion.
2. Long bone nonunions when an autograft is not feasible and alternative treatments have failed.

The use of bone morphogenic protein is considered investigational for all other indications, such as multiple level lumbar fusions, fusions of the thoracic or cervical spine, augmentation of bone autografting, restorative dental surgery, craniofacial surgery and fracture nonunions of other sites. (Regence 2002)

Conclusions

Bone morphogenetic proteins 2 and 7 have been studied in treating nonunion of long bones. Several randomized controlled trials have compared BMP to autograft in the treatment of both open and closed tibial fractures. Patients with closed tibial fractures showed similar outcomes regardless of treatment regimen. Tibial nonunions also showed similar outcomes. Data from one randomized controlled trial suggested that open tibial fractures benefited from treatment with BMP compared to standard of care.

Patients who received the BMP implants tended to have shorter operative times and shorter hospital stays. However, the differences were not always statistically significant. In addition, patients with BMP implants did not experience donor site pain in comparison to autograft patients.

Two, small case series studies have been published in the area of femoral nonunion. The patients in the two studies tended to have complex fractures that had positive outcomes following BMP treatment. However, it cannot be determined whether BMP had a significant causal effect on outcomes since the studies did not include comparison groups.

Randomized controlled trials of BMP in spinal fusions compared to autograft have shown similar outcomes regardless of treatment. In addition, patients with BMP implants did not experience donor site pain in comparison to autograft patients.

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Appendix A: Additional Publications by Burkus

1. Burkus conducted a prospective, randomized, non-blinded trial evaluating radiographic outcomes of patients who underwent a single-level anterior interbody fusion with the LT-LCAGE device. (Burkus 2003)

42 patients were randomly assigned from a table of random numbers to receive either the LT-CAGE device with rhBMP-2 on an absorbable collagen sponge carrier or the LT-CAGE device with autogenous iliac crest bone graft.

Two independent radiologists evaluated plain radiographs and thin-cut computed tomographic (CT) scans for patterns of osteoinduction at 2 days and at 6, 12, and 24 months after surgery. The study defined fusion as:
1. absence of radiolucent lines covering more than 50% of either implant
2. translation of 3 mm or less
3. angulation of less than 5 degrees on flexion-extension lateral radiographs, and
4. continuous trabecular bone growth connecting the vertebral bodies.

On CT scans, fusion was defined as increased density in the cages and the presence of continuous trabecular bone formation through both of the cages.

Study Population: The study included patients with symptomatic degenerative lumbar spondylosis at L4-L5 or L5-S1. Patients also had disabling low back pain, leg pain, or both that lasted at least 6 months and had not resolved with nonoperative treatment.

Patients were excluded due to osteoporosis, spinal conditions other than degenerative disc disease, multilevel spondylosis, at least Grade 2 spondylolisthesis, symptomatic spondylosis outside the L4-L5 or L5-S1 disc space levels, weight more than 40% above ideal body weight, chronic steroidal or nonsteroidal anti-inflammatory medications use, or a history of disc space infection.

Demographic data

	rhBMP-2	Control Bone Graft
Number of patients	22	20
Average age (years)	41.7	44.2
Tobacco use within 6 months of surgery	4 (18%)	2 (10%)

Three patients were eliminated for failure to complete the 24-month follow-up.

Results: At 12 months, one control patient was identified as having a pseudoarthrosis.

Bone Density Measurements within the Interbody Fusion Device

Bone Density (HU)	Investigational Group	Control Group
Immediate post-operative		
n	16	12

	Mean	179.0	541.3
6 months			
	n	20	18
	Mean	322.1	574.6
12 months			
	n	21	19
	Mean	427.1	667.1
24 months			
	n	20	18
	Mean	442.9	628.1

Progression of densities in the cages correlated with evidence of fusion on standard plain radiographic measurements.

Increases in bone density were found in the autograft control group, but the rates of change were less compared to the rhBMP-2 group. The radiographic densities in the cages of the rhBMP-2 group at 24 months did not reach those of the autograft control group after initial implantation because cancellous and cortical bone were packed into autograft group cages.

The rates of new bone formation in the rhBMP-2 group exceeded those of the autograft control group. All new bone formation outside the cages occurred within the disc space, and no ectopic bone formation was noted.

Conclusion: High fusion rates associated with new bone formation inside and outside the cages can be achieved without harvesting bone from the iliac crest and without device-related adverse events.

2. Burkus also reported clinical findings from a trial comparing 24 BMP-2 patients to 22 autogenous iliac crest bone graft patients. (Burkus 2002a)

Data from the Oswestry Low Back Pain Disability Questionnaire, Short Form 36, neurologic status, work status, patient satisfaction, back, leg, and graft-site pain questionnaires were collected at 6 weeks, and 3, 6, 12, and 24 months.

Two blinded radiologists examined radiographs and CT scan. The study defined a successful fusion as meeting all of the following:
1. bridging trabecular bone connecting the two vertebral bodies either through the dowels or around the dowels
2. no angular motion of 5 degrees or more
3. no sagittal translation of more than 3 mm
4. no radiolucencies that involved more than half of the interfaces between the dowels and the host vertebral end plates

Study Population: The study included 46 patients with degenerative disc disease at L4-L5 or L5-S1 levels. The patients' primary symptoms were low back pain with or without

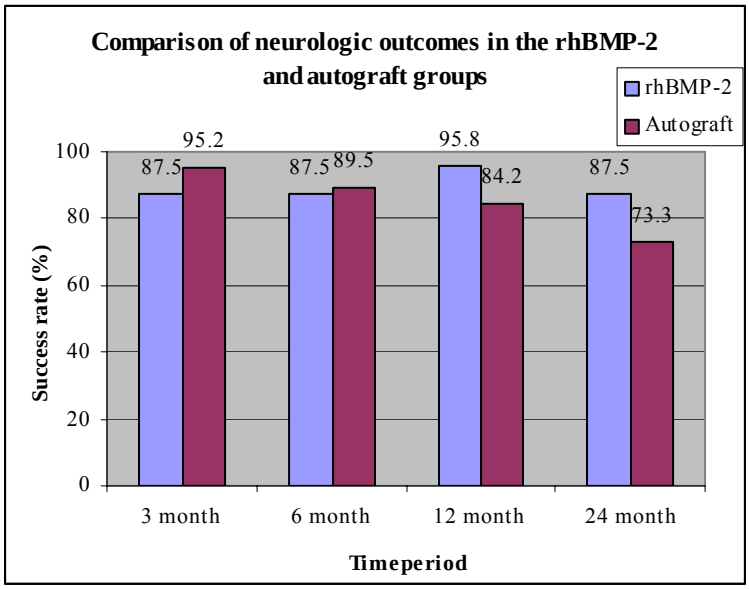
leg pain or sciatica. They scored 35 points or more on the Oswestry Low Back Pain Disability Index and had disabling symptoms for a minimum of 6 months despite conservative treatment.

The required correlative radiographic findings included segmental angulation of 5 degrees or translation of 4 mm, or both; osteophyte formation; decreased disc height of at least 50%; thickening of ligamentous tissue, disc protrusion and herniation.

The study excluded patients due to medical conditions requiring medications such as steroids or nonsteroidal anti-inflammatory drugs (NSAIDS) that interfere with fusion.

Results: One control patient was lost to follow-up and 1 patient died in a fire after surgery. As a result, 20 control patients were followed for a minimum of 24 months after surgery.

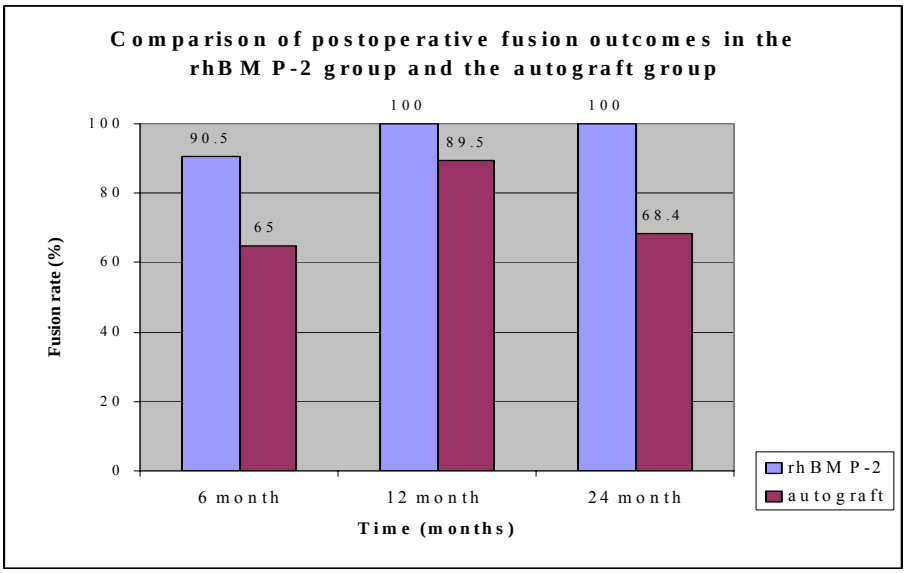
At discharge, graft site pain was highest (11.3) for control patients. The pain averaged 2.2 at 24 months in these patients.



Improvement in Pain by Treatment Group and Follow-up Time

	n		Back Pain Improvement		Leg Pain Improvement	
	rhBMP-2	Autograft	rhBMP-2	Autograft	rhBMP-2	Autograft
preop	24	22	16.3	16.3	12.8	14.6
3 months	24	21	7.9	10.9	6.2	8.3
6 months	24	20	6.8	9.9	5	6.1
12 months	24	19	7.4	9.2	5.5	8.1
24 months	24	17	7.4	10.9	6.3	11.5

Average blood loss was less in the investigational group than in the control group. The average hospital stay was similar in both groups.



Investigational group had significantly greater improvement in Oswestry scores than the control group. At 3 months, 71% of the rhBMP-2 group and 43% of the control group showed an improvement of at least 15 points in the disability score. At 12 months, 83% of the rhBMP-2 group and 58% of controls improved more than 15 points.

45.8% of the rhBMP-2 group and 40.9% the control group were working before surgery. At 24 months after surgery, 66.7% of rhBMP-2 subjects and 35.0% of controls were working.

At 24 months, the success rate was more than 83% in the rhBMP-2 group for 3 questions about patient satisfaction. The success rate in the control group ranged from 55% to 65%.

One investigational and 3 control patients underwent supplemental posterior fixation procedures after their primary surgeries.

Researchers did not observe any adverse events related to the rhBMP-2 or the collagen sponge carrier.

Conclusion: rhBMP-2 was shown to be a promising method of facilitating anterior intervertebral spinal fusion and of decreasing pain and improving clinical outcomes after anterior lumbar fusion surgery with allograft bone dowels.

Appendix B: Additional Publications of Studies Conducted for FDA Approval

1. Kleeman's data come from a single site selected as part of a multicenter, prospective, controlled, nonrandomized study of rhBMP-2 performed under FDA device exemption. (Kleeman 2001)

Study Population: The study included 22 patients with an average age of 38 years and an average duration of symptoms of 50 months. Twelve patients (55%) were involved in workers' compensation or litigation. Two patients were smokers. Seven patients underwent fusion at L4-L5 whereas 15 patients underwent fusion at L5-S1.

Results: Twenty-one patients were available for follow-up. Patients' operative time averaged 102 minutes. Average operative time for L4-L5 fusion was 131 minutes, and L5-S1 averaged 88 minutes. Researchers observed contiguous ossification in all 21 patients at 6 months without evidence of motion or lucent zones at the implant-bone interface. At 12 month, 48% of patients reported return to full function.

Outcomes by Follow-up Time

	Preop	6 months	12 months
Oswestry Score	47	16	11
No. (%) patients who improved >15 points on Oswestry		18/21 (86%)	21/21 (100%)
Average functional capacity (12' lift in lbs)	32	43	50
Average VAS	7.7	2.1	1.9
No. (%) employable patients who returned to work		16/18 (89%)	18/18 (100%)

Conclusion: Discogenic back pain can be effectively treated with a laparoscopic anterior lumbar interbody fusion using rhBMP-2 in place of autogenous bone.

2. Boden's multicenter, nonblinded, randomized pilot study of rhBMP-2 was conducted under FDA IDE. (Boden 2000)

Patients were randomized in a 3:1 investigation:control block fashion to receive anterior lumbar arthrodesis with 2 NOVUS LT tapered interbody fusion devices filled with autogenous iliac crest bone (n=3) or hBMP-2 (n=11). Cages were inserted via standard laparascopic or open anterior surgical techniques.

Data from the SF-36 and Oswestry Low Back Pain Disability Questionnaire were collected before surgery and at 6 weeks, 3 months, 6 months, 12 months, and 24 months after surgery. Clinical success on the Oswestry was defined as an improvement of at least a 15% over the preoperative score.

Results: Significant differences in operative time resulted from harvesting iliac crest bone in control patients. In addition, all 4 laparoscopic patients were in the investigational group.

Surgical Procedure/Hospital Stay Information

Category	Investigational (n=11)	Control (n=3)
Operative Time (hrs)	1.9	3.3
Blood Loss (mL)	95	167
Hospital Stay (days)	2.0	3.3

Number of Patient (%) with Solid Fusions According to CT Scan and Radiograph

Follow-up	Investigational (n=11)	Control (n=3)
3 months	10 (90.9%)	2 (66.7%)
6, 12, 24 months	11 (100%)	2 (66.7%)

Oswestry Low Back Pain Disability Questionnaire Scores

Time Point	RhBMP-2 Score	Control Score	RhBMP-2 No. (%) Successful	Control No. (%) Successful
Preoperative	38.9	34.7	0/2 (0.0%)	0/1 (0.0%)
3 months	29.8	42.7	6/11 (54.7%)	0/3 (0.0%)
6 months	26.9	28.0	7/11 (63.6%)	2/3 (66.7%)
12 months	17.7	27.3	10/11 (90.9%)	2/3 (66.7%)
24 months	13.5	20.0	10/11 (90.9%)	2/3 (66.7%)

The mean improvement in Oswestry score for the rhBMP-2 patients was 25 points (71.8%) at 24 months, compared with a 15-point (54.1%) improvement in control patients. The difference was not significant.

At 3 months, 6 of 11 (54.6%) rhBMP-2 patients had returned to work. At 6 months, 8 of 11 (72.7%) returned. Three patients not working 6 months after surgery had not been working before treatment. Two of the 8 patients working at 6 months had not been working before treatment. At 12 and 24 months, 9 of 11 patients working. Two control patients were working at 6, 12, and 24 months. One control subject not working after surgery had not been working before treatment.

The researchers did not observe adverse events related to the cage or graft material. Furthermore, there were no clinically relevant differences in blood count or blood chemistry results between groups. None of the rhBMP-2 patients had increased rhBMP-2 antibody titers after surgery. Three patients had increased antibovine collagen Type I titers, but no patients developed antibodies for human collagen Type I.

Conclusion: The arthrodesis occurred more reliably in patients treated with rhBMP-2-filled fusion cages than in controls treated with autogenous bone graft, although the sample size as limited. There were no adverse events related to rhBMP-2.

Appendix C

Definitions for Classification of Evidence

Rating of recommendation	Translation of evidence to recommendations	Rating of Therapeutic Article
(note: technology assessment ratings in parentheses) A = Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population	Level A rating requires at least two consistent Class I studies*	**Class I:** Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required: a) primary outcome(s) is/are clearly defined b) exclusion/inclusion criteria are clearly defined c) adequate accounting for drop-outs and cross-overs with numbers sufficiently low to have minimal potential for bias d) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
B = Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population	Level B rating requires at least one Class I study or two consistent Class II studies	**Class II:** Prospective matched group cohort study in a representative population with masked outcome assessment that meets a-d above OR a RCT in a representative population that lacks one criteria a-d.
C = Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population	Level C rating requires at least one Class II study or two consistent class III studies	**Class III:** All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**
U = Data inadequate or conflicting. Given current knowledge, treatment (test, predictor) is unproven	Studies not meeting criteria for class I-class III	**Class IV:** Evidence from uncontrolled studies, case series, case reports, or expert opinion.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria met, 2) magnitude of effect ≥5, and 3) narrow confidence intervals (lower limit >2).

***Objective outcome measurement*—an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).